Summary of

NeuroRestore – a novel therapeutic concept for the treatment of depression?

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Psychopharmacol 2023: *https://link.springer.com/article/10.1007/s00213-023-06410-x*
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Depression is a life-threatening psychiatric disorder and a major public health concern worldwide with an incidence of 5% and a lifetime prevalence of 15–20%. Moreover, depression is associated with disability, decreased quality of life, increased health-related costs and is considered a major risk factor for many diseases, including cardiovascular, metabolic and neuropsychiatric disorders. Although the currently available antidepressants provide a measurable degree of therapeutic relief, approximately 50% of individuals diagnosed with MDD do not respond adequately to treatment with conventional antidepressants. Therefore, there is a pressing medical need to develop novel antidepressants that are capable of effectively relieving the depressive symptomology.

Brain-Derived Neurotrophic Factor (BDNF) is a protein that plays a crucial role in the growth, development, and maintenance of neurons in the brain. It is involved in promoting the survival of existing neurons and the growth of new neurons and synapses. BDNF is often considered to be a key player in the plasticity of the brain, which refers to its ability to adapt and change in response to experiences and environmental factors.

Research suggests that BDNF levels and functioning are disrupted in individuals with depression. In fact, some studies have shown that individuals with depression tend to have lower levels of BDNF in their brain and blood compared to those without depression. Reduced BDNF levels have been associated with the atrophy (shrinkage) of certain brain regions, particularly in areas important for mood regulation and cognitive functioning. BDNF is also involved in promoting neuroplasticity, which is the brain's ability to reorganize itself by forming new connections between neurons. Neuroplasticity is important for learning, memory, and adapting to stress. Lower BDNF levels might contribute to reduced neuroplasticity and hinder an individual's ability to cope with stress and recover from negative experiences, which are factors relevant to depression.

Interestingly, some antidepressant medications and therapeutic interventions are believed to work, at least in part, by increasing BDNF levels. For example, certain classes of antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), are thought to boost BDNF production. Physical exercise and certain psychotherapies have also been shown to increase BDNF levels, potentially contributing to their antidepressant effects. Furthermore, recent data suggest that different classes of antidepressants, both ketamine and SSRI's such as fluoxetine, mediate their antidepressant effects through TrkB, the receptor of BDNF (Casarotto et al. Cell, 2021). In recent years, psychedelics, such as psilocybin (found in certain

mushrooms), LSD, and MDMA, have gained attention for their potential role in treating depression and other mental health conditions. Interestingly, a recent article in Nature show that psychedelics such as LSD also seem to be dependent on BDNF/TrkB to mediate their antidepressant effects (Moliner et al. Nature, 2023).

Compounds in AlzeCure's NeuroRestore platform are so called Trk-PAMs, which stimulate specific signaling pathways in the central nervous system known as neurotrophins, including NGF (Nerve Growth Factor) and BDNF. The leading drug candidate in the platform, ACD856, has recently completed clinical phase I studies and demonstrated positive effects that support continued development of the program. Based on NeuroRestore compounds' ability to enhance BDNF signaling, preclinical studies were conducted to assess their potential antidepressant effects. The results demonstrate that ACD856 and other compounds from this class show potent antidepressant effects in several animal models, with effects similar or better than SSRI's (Madjid et al. Psychopharmacology, 2023). Moreover, the data showed that these effects were mediated by BDNF/TrkB signaling and also replicated earlier findings, showing that both ketamine and SSRI's such as fluoxetine, mediate their antidepressant effects through TrkB. Interestingly, combining fluoxetine or ketamine with a NeuroRestore compound resulted in additive or synergistic effects suggesting possible combinatorial use in future clinical studies.
Further preclinical studies also reveal that ACD856 induces rapid and transient release of relevant signal substances in the brain. In summary, the presented results indicate an interesting potential for NeuroRestore compounds as a novel class of antidepressants.

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